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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/108,673	07/01/1998	CHIN-LEOU TENG	ISIS-3105	2703

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PAUL K LEGAARD
WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS
ONE LIBERTY PLACE 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	40

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/108,673	Applicant(s) Teng et al
	Examiner William Sandals	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 6, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *25-27, 44-50, 53-55, 57-64, 66-77, and 79-82* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-27, 44-50, 53-55, 57-64, 66-77, and 79-82* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

2. The declaration of Mark K. Wedel, M.D., J.D. under 37 CFR 1.132 filed in Paper No. 39 on October 9, 2002 is insufficient to overcome the rejection of claims 25-27, 66-77 and 79-82 based upon USC 112, first paragraph, enablement, as set forth in the last Office action because: the declaration is silent as to the formulation of the antisense nucleic acid with respect to the penetration enhancers and modified nucleic acid limitations of the instant claims. Further, the data presented in exhibits D, E and F are uninterpretable as submitted.

Response to Arguments

3. Arguments presented in Paper No. 38, filed October 9, 2002 have overcome the rejections of the claim 61 over JP 357080314 A (Kitao) and WO 97/05903 (Watts et al.) under 35 USC 102 in the previous office action, and the rejections are withdrawn.

4. Arguments presented in Paper No. 38, filed October 9, 2002 have overcome the rejections of the claims 25-27, 66-77 and 79-82 based upon USC 112, first paragraph, enablement, in the previous office action, and the rejections are withdrawn.

5. Arguments presented in Paper No. 38, filed October 9, 2002 have overcome the rejections of the claims 25-27, 66-77 and 79-82 based upon 35 USC 103 in the previous office action, and the rejection is withdrawn.

6. New grounds for rejection are presented below.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 25-27, 66-77 and 79-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of investigation of the role of a gene or gene product in an animal (which may be other than a human), does not reasonably provide enablement for a method of treatment involving gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of delivering (enhancing penetration) of a composition containing an nucleic acid (antisense) to an animal where the antisense decreases the expression of a cellular adhesion protein or the rate of cellular proliferation. The specification and claims are directed to a method of delivering (enhancing penetration) of a nucleic acid (antisense) a method of treating with a nucleic acid in an animal having or suspected of having a disease or

disorder that is treatable in whole or in part with one or more nucleic acids delivered to the animal via the enteral route.

The Specification does not teach one of ordinary skill in the art how to use an antisense nucleic acid in a method to treat with a gene or gene product in an animal (which may be other than a human). Treatment with antisense nucleic acids is a new and developing art involving gene therapy which is highly unpredictable. While the Specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway which is a step toward a method of treatment with nucleic acids (antisense), it does not teach one of ordinary skill in the art how to treat with a gene or gene product with nucleic acids (antisense) since the practice of the treatment is highly unpredictable, and would require specific teachings to guide the ordinary skilled artisan how to make and use the claimed invention. As such, specific teachings must be present in the Specification to support any claims to treatment or investigation in an animal with a nucleic acid (antisense). Since these teachings are not found in the instant specification, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivery via the enteral route of a nucleic acid (antisense) to an animal

and predictably treating with the delivery of the nucleic acid (antisense) in the animal. Treatment of an animal with a nucleic acid (antisense) is a new and developing art, and as such requires detailed teachings on how to use such a nucleic acid.

b- The specification teaches the delivery of a nucleic acid via the enteral route to the blood and generally into the internal organs of an animal by cannula delivery of nucleic acid (antisense) to the small intestine of a rat. There are no teachings of treatment with a nucleic acid (antisense).

c- The nature of the invention is complex. Treatment of animals with nucleic acid (antisense) is a new and developing art as taught in Gewirtz et al. (see the entire article). Gewirtz et al. taught the difficulties of therapy with nucleic acids such as antisense oligodeoxynucleotide, stating that there are two major problems which must be overcome. First, the nucleic acid must find its cellular target. Second, it must then find and act on its intracellular target. The specification does not teach one of ordinary skill in the art how to direct the nucleic acid to its cellular target nor how the nucleic acid would then act on its intracellular target.

d- The state of the prior art as taught by Gura (see especially page 575, column 1, second paragraph, and page 576, third paragraph to the end of the article) demonstrates some of the difficulties associated with nucleic acid pharmaceutical therapy, stating "[b]ut the biggest concern is that antisense compounds simply don't work the way researchers once thought they did"...."Besides not always working by 'true antisense mechanisms,' the synthetic oligonucleotides have also caused side effects in experimental animals."

e- The state of the art as recited in Stull et al. (see especially pages 476-478) taught that the stability, affinity, efficiency and subcellular distribution of the nucleic acids in the host animal are all areas of uncertainty and need careful study and analysis before any nucleic acid therapeutic modality can be understood and consistently applied. Also, Agrawal et al. taught the delivery of synthetically modified nucleic acids administered to rats via the oral route. However, the nucleic acids had been specifically modified to resist nuclease digestion. No gene therapy was demonstrated by Agrawal et al.

f- The teaching of absorption into the blood and internal organs of the nucleic acids in the instant Specification does not demonstrate any targeting of the nucleic acid to a cell or to intracellular targets as recited by Gewirtz et al., nor does the Specification address any of the issues raised by Gura or Stull et al. Therefore, no predictable pharmaceutical effect has been demonstrated.

g- Branch et al. (TIBS, Feb. 1998) teach at the abstract that antisense is "difficult to produce" and "their ability to eliminate the function of a single gene has never been proven". Agrawal et al. (Molecular Medicine Today, Vol. 6, pp 72-81, February 2000, at the Introduction and "Cellular uptake facilitators for in vitro studies" at pages 79-80) teach that antisense molecules are unpredictable in their use for in-vivo applications. For the reasons stated by Gewirtz et al., Gura, and Stull et al. Agrawal et al. and Branch et al. the unpredictability of therapeutic applications of nucleic acids is very high. The burden thus falls to the instant claims

and specification provide the necessary teachings to overcome this lack of teaching in the prior art. No such teaching is provided in the instant claims and specification.

h- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

9. Arguments set forth in Paper No. 34, page 8 assert that the invention defined by the claims must be enabled, and that not all inventions set forth in the specification need be enabled. This is true. The invention as set forth in the claims is not enabled as discussed above. Delivery of an antisense nucleic acid to the alimentary canal of an animal lacks a utility per se. The delivery of an antisense nucleic acid across the intestinal mucosa also does not have a utility, since the purpose of delivering an antisense nucleic acid across the intestinal mucosa is one step in the delivery of the antisense nucleic acid for some real-world purpose, such as the stated treatment or investigation of the role of a gene or gene product. Therefore, lack of enablement does not concern delivery of an antisense across the intestinal mucosa.

10. The declaration of Dr. Teng is discussed in the office action mailed July 16, 2002. For reasons of record, the declaration is not found sufficient to overcome the rejection.

11. Arguments presented in Paper No. 38 assert that the declaration of Dr. Mark K. Wedel supports the assertion that antisense technology is predictable. For the reasons stated above, the declaration was not sufficient to overcome the rejection.

12. Arguments presented in Paper No. 38 assert that the declaration of Dr. Mark K. Wedel supports the assertion that antisense technology can be used in methods of treating a disease. The declaration of Dr. Mark K. Wedel is insufficient to support such a claim for the reasons stated above.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 61 and 62 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,707,648 (Yiv).

Yiv (see especially columns 2-8, 12-15 and the claims) taught a composition comprising a nucleic acid (antisense) and capric acid or lauric acid in a pharmaceutically acceptable formulation. The nucleic acid has a modified nucleobase or a modified sugar residue.

Response to Arguments

15. Arguments presented in Paper No. 38 regarding the Yiv reference discuss claims which are no longer present in the rejection. Therefore, the arguments are moot with regard to the present rejection.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,707,648 (Yiv) (of record)in view of US 5,843,738 (Bennett et al.) (of record).

The claims are drawn to a composition comprising a nucleic acid (antisense) and capric acid or lauric acid in a pharmaceutically acceptable formulation. The nucleic acid has a modified nucleobase or a modified sugar residue. The antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

Yiv (see especially columns 2-8, 12-15 and the claims) taught a composition comprising a nucleic acid (antisense) and capric acid or lauric acid in a pharmaceutically acceptable formulation. The nucleic acid has a modified nucleobase or a modified sugar residue.

Yiv did not teach that the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

Bennett et al. teach at column 3, line 63 bridging to column 4, lines 34, and columns 9-10 a composition of an antisense nucleic acid and a lipid formulation (fatty acid) where the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Yiv with Bennett et al. to produce the instant claimed invention. The combination of Yiv with Bennett et al. make obvious the composition because each of Yiv and Bennett et al. taught a composition comprising an antisense nucleic acid and a fatty acid. Bennett et al. provides additional teachings on the use of antisense nucleic acid to decrease the expression of a cellular adhesion protein or the rate of cellular proliferation *in vitro* and *in vivo*.

One of ordinary skill in the art would have been motivated to combine the teachings of Yiv with Bennett et al. to produce the instant claimed invention because Bennett et al. taught that antisense nucleic acid as taught by Yiv and Bennett et al. is useful and desirable for decreasing the expression of a cellular adhesion protein or the rate of cellular proliferation. Further, a

person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Yiv with Bennett et al.

18. Claims 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yiv with Bennett et al. as applied to claims 61-63 above, and further in view of US 5,948,898 (Dean et al.).

The claims are as described above and also where the nucleic acid has a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

Yiv and Bennett et al. taught the invention as described above. Bennett et al. teach at columns 9-10 the desirable and beneficial modification of nucleic acids with alkyl substitutions.

Yiv and Bennett et al. did not teach that the nucleic acid has a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

Dean et al. teach at columns 6 and 8-10 a composition of an antisense nucleic acid and a lipid formulation (fatty acid) where the nucleic acid is modified with an alkyl substitution, specifically, a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification to increase affinity of the antisense for its target and for the increased resistance to nuclease.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Yiv and Bennett et al. with Dean et al. to produce the instant claimed invention. Yiv, Bennett et al. and Dean et al. make obvious the instant claimed composition because each of Yiv, Bennett et al. and Dean et al. taught a composition comprising an antisense nucleic acid and a fatty acid. Bennett et al. teach an alkyl substitution of antisense nucleic acids and Dean et al. teaches an alkyl substitution of nucleic acids where the nucleic acid is an antisense nucleic acid which has a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

One of ordinary skill in the art would have been motivated to combine the teachings of Yiv and Bennett et al. with Dean et al. to produce the instant claimed invention because each of Yiv and Bennett et al. with Dean et al. teach the combination of antisense nucleic acids with fatty acids. Bennett et al. teach the desirable and beneficial alkyl substitution of an antisense nucleic acid, and Dean et al. teach at column 6, lines 22-42 the desirable and beneficial use of an alkyl substitution of an antisense nucleic acid which is a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification for the desirable benefit of increasing affinity of the antisense for its target and for the increased resistance to nuclease. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Yiv, Bennett et al. and Dean et al.

19. Claims 44-49, 53-55 and 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of US 5,707,648 (Yiv) in view of US 5,948,898 (Dean et al.).

The claims are drawn to a composition comprising a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue and a method of using the composition for (delivering) enhancing penetration of an antisense nucleic acid across the alimentary canal. The nucleic acid may be modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification. The two fatty acids may be capric acid and lauric acid. The composition may further comprise a carrier compound. The composition may be water based or propylene glycol based and may comprise less than about 8% water. The composition may further comprise a bile salt. The oligonucleotide may be in the form of a prodrug. The carrier compound may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

Yiv taught the invention as described above. Yiv also taught at columns 5-8 and 12-14 that the two fatty acids may be capric acid and lauric acid, the composition may further comprise a carrier compound, the composition may be water based or propylene glycol based and may comprise less than about 8% water, the composition may further comprise a bile salt and the oligonucleotide may be in the form of a prodrug.

Yiv did not teach that the nucleic acid may be modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification, nor that the carrier compound may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

The instant specification teaches at page 12, lines 19-37 that it was well known in the prior art that a carrier compound for nucleic acids may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid making the use of these carrier compounds prima facie obvious to one of ordinary skill in the art.

Dean et al. teach at columns 6 and 8-10 a composition of an antisense nucleic acid and a lipid formulation (fatty acid) where the antisense nucleic acid may be modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification to increase affinity of the antisense for its target and for the increased resistance to nuclease.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Yiv with Dean et al. to produce the instant claimed invention. Yiv and Dean et al. make obvious the composition because each of Yiv and Dean et al. taught a composition comprising an antisense nucleic acid and a fatty acid. Dean et al. provides additional teachings on the usefulness of an antisense nucleic acid which has a 5-

methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

One of ordinary skill in the art would have been motivated to combine the teachings of Yiv with Dean et al. to produce the instant claimed invention. Dean et al. teach at column 6, lines 22-42 the desirable and beneficial modification of the antisense nucleic acid as taught by Yiv and Dean et al. with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification for the desirable and beneficial increase in affinity of the antisense for its target and for the increased resistance to nuclease. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Yiv and Dean et al.

20. Claims 44-50, 53-55 and 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yiv with Dean et al. as applied to claims 44-49, 53-55 and 57-60 above, and further in view of US 5,843,738 (Bennett et al.).

The claims are as described above and also where the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

Yiv and Dean et al. taught the invention as described above. Yiv also taught that the composition is useful to facilitate delivery of a nucleic acid to the alimentary canal of an animal.

Yiv and Dean et al. did not teach that the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

Bennett et al. teach at column 4, lines 24-29, and columns 9-10 a composition of an antisense nucleic acid and a lipid formulation (fatty acid) where the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation. Bennett et al. teach at column 3, line 62 bridging to column 4, line 34, at the examples and in figures 5-16 the useful delivery of a composition of antisense nucleic acid and a fatty acid to study the effects of the composition *in vitro* and *in vivo*.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Yiv and Dean et al. with Bennett et al. to produce the instant claimed invention. Yiv, Bennett et al. and Dean et al. make obvious the composition because each of Yiv, Bennett et al. and Dean et al. taught a composition comprising an antisense nucleic acid and a fatty acid. Bennett et al. provides additional teachings on the use of a composition comprising antisense nucleic acid and a fatty acid to investigate the decrease of expression of a cellular adhesion protein or the rate of cellular proliferation in cells *in vitro* and *in vivo*.

One of ordinary skill in the art would have been motivated to combine the teachings of Yiv and Dean et al. with Dean et al. to produce the instant claimed invention because Bennett et al. taught that a composition comprising an antisense nucleic acid and a fatty acid as taught by Yiv, Dean et al. and Bennett et al. is useful and desirable for investigating a composition

comprising an antisense nucleic acid and a fatty acid which decreases the expression of a cellular adhesion protein or the rate of cellular proliferation. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Yiv with Bennett et al.

21. Claims 25-27, 66-73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of US 5,707,648 (Yiv) in view of US 5,948,898 (Dean et al.).

The claims are drawn to a method of delivering (enhancing penetration) of a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form across the intestinal mucosa, wherein the nucleic acid (antisense) has a modified nucleobase or modified sugar residue and a method of using the composition for (delivering) enhancing penetration of an antisense nucleic acid across the alimentary canal. The nucleic acid (antisense) is modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification. The two fatty acids may be capric acid and lauric acid. The composition may further comprise a carrier compound. The composition may be water based or propylene glycol based and may comprise less than about 8% water. The composition may further comprise a bile salt. The oligonucleotide may be in the form of a prodrug. The carrier compound may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

Yiv taught at columns 2-8, 12-15 and the claims a method of delivering (enhancing penetration) of a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form across the intestinal mucosa, wherein the nucleic acid (antisense) has a modified nucleobase or modified sugar residue and a method of using the composition for (delivering) enhancing penetration of an antisense nucleic acid across the alimentary canal. Yiv taught at columns 5-8 and 12-14 that the two fatty acids may be capric acid and lauric acid, the composition may further comprise a carrier compound, the composition may be water based or propylene glycol based and may comprise less than about 8% water, the composition may further comprise a bile salt and the oligonucleotide may be in the form of a prodrug.

Yiv did not teach that the nucleic acid may be modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification, nor that the carrier compound may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

The instant specification teaches at page 12, lines 19-37 that it was well known in the prior art that a carrier compound for nucleic acids may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid making the use of these carrier compounds prima facie obvious to one of ordinary skill in the art.

Dean et al. teach at columns 6 and 8-10 a method of introducing a nucleic acid (antisense) and a lipid formulation (fatty acid) via the alimentary canal (oral or rectal) where the nucleic acid

(antisense) is modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification to increase affinity of the antisense for its target and for the increased resistance to nuclease.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Yiv with Dean et al. to produce the instant claimed invention. Yiv and Dean et al. make obvious the method of delivering (enhancing penetration) of a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form across the intestinal mucosa because each of Yiv and Dean et al. taught a method of delivering an antisense nucleic acid and a fatty acid via the alimentary canal. Dean et al. provides additional teachings on the use of an antisense nucleic acid which has a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

One of ordinary skill in the art would have been motivated to combine the teachings of Yiv with Dean et al. to produce the instant claimed invention because Dean et al. teach at column 6, lines 22-42 the desirable and beneficial use of an antisense nucleic acid which has a 5-methyl-cytosine substitution, a phosphorothioate linkage and a 5-methyl-cytosine substitution, or a phosphorothioate linkage and a 2'-methoxyethoxy modification for the desirable benefit of increasing affinity of the antisense for its target and for the increased resistance to nuclease. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Yiv and Dean et al.

22. Claims 25-27, 66-73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yiv with Dean et al. as applied to claims 25-27, 66-77 and 79-82 above, and further in view of US 5,843,738 (Bennett et al.).

The claims are as described above and also where the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

Yiv and Dean et al. taught the invention as described above.

Yiv and Dean et al. did not teach that the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

Bennett et al. teach at column 4, lines 24-29, and columns 9-10 a composition of an antisense nucleic acid and a lipid formulation (fatty acid) where the antisense nucleic acid decreases the expression of a cellular adhesion protein or the rate of cellular proliferation. Bennett et al. teach at column 3, line 62 bridging to column 4, line 34, at the examples and in figures 5-16 a method of delivery of a composition of antisense nucleic acid and a fatty acid to investigate the effects of the composition in cells in culture and in animals *in vitro* and *in vivo*.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Yiv and Dean et al. with Bennett et al. to produce the instant claimed invention. Yiv, Dean et al. and Bennett et al. make obvious the method of delivering (enhancing penetration) of a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form across the intestinal mucosa because each of Yiv, Dean et al. and Bennett et al. taught a method for delivering a composition to an animal comprising an

antisense nucleic acid and a fatty acid. Bennett et al. provides additional teachings on the use of a composition comprising antisense nucleic acid and a fatty acid to investigate the use of an antisense nucleic acid which decreases expression of a cellular adhesion protein or the rate of cellular proliferation *in vitro* or *in vivo*.

One of ordinary skill in the art would have been motivated to combine the teachings of Yiv and Dean et al. with Bennett et al. to produce the instant claimed invention because Bennett et al. taught that a composition comprising an antisense nucleic acid and a fatty acid as taught in each of Yiv, Dean et al. and Bennett et al. is useful and desirable for investigation of an antisense nucleic acid for the desirable benefit of decreasing expression of a cellular adhesion protein or the rate of cellular proliferation. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Yiv and Dean et al. with Bennett et al.

Conclusion

23. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
November 2, 2002

TERRY MCKELVEY
PRIMARY EXAMINER